AFRL-HE-BR-TR-2004-0015

United States Air Force Research Laboratory

A LABORATORY EVALUATION OF ZALEPLON FOR DAYTIME SLEEP

Jeffery Whitmore

HUMAN EFFECTIVENESS DIRECTORATE
BIOSCIENCES AND PROTECTION DIVISION
FATIGUE COUNTERMEASURES BRANCH
2504 GILLINGHAM DRIVE
BROOKS CITY-BASE TX 78235

Joseph Fischer, Jr.

GENERAL DYNAMICS
2504 GILLINGHAM DRIVE, STE 25
BROOKS CITY-BASE, TX 78235

Emily Barton
Rebecca Cardenas
William Storm

NTI, Inc.
2504 GILLINGHAM DRIVE, STE 25
BROOKS CITY-BASE, TX 78235

May 2004

NOTICES

This report has been reviewed and is approved for publication.

//SIGNED//

JEFFERY N. WHITMORE
Project Scientist

//SIGNED//

F. WESLEY BAUMGARDNER, Ph.D.
Deputy, Biosciences and Protection Division

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
May 2004	Interim	Jan 2003 - Jan 2004

4. TITLE AND SUBTITLE
A Laboratory Evaluation of Zaleplon for Daytime Sleep

5a. CONTRACT NUMBER
F41624-97-D-6004

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER
62202F

6. AUTHOR(S)
Whitmore, Jeffery, Fischer Jr, Joseph, Barton, Emily, Cárdenas, Rebecca, Storm, William

5d. PROJECT NUMBER
7757

5e. TASK NUMBER
P9

5f. WORK UNIT NUMBER
04

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

General Dynamics
2504 Gillingham Dr
Brooks City-Base, TX 78235

NTI, Inc.
2504 Gillingham Dr
Brooks City-Base, TX 78235

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Air Force Research Laboratory
Human Effectiveness Directorate
Biosciences and Protection Division
Fatigue Countermeasures Branch
Brooks City-Base, TX 78235

10. SPONSOR/MONITOR'S ACRONYM(S)
AFRL/HE

11. SPONSOR/MONITOR'S REPORT NUMBER(S)
AFRL-HE-BR-TR-2004-0015

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release, distribution unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT
Rationale: Zaleplon appears to be a prime candidate for assisting individuals in obtaining sleep in situations not conducive to rest. *Objectives:* The primary objective of this study was to determine whether zaleplon (10-mg) effectively promoted sleep during the daytime in well rested individuals when compared to placebo. A secondary objective was to see if, while not expected, the use of zaleplon impacted the performance of these well rested individuals upon awakening. *Methods:* Twelve participants, 6 males and 6 females, participated in this study. The study was conducted using a repeated measures design with two within-subject factors: drug (placebo/zaleplon) and trial (hourly testing during waking hours). Each participant experienced both drug conditions, with drug administration being counterbalanced and double-blinded. During a 3.5 hour nap following drug administration, polysomnographic variables were recorded to measure quality of sleep. Performance measures (cognition, memory, balance, and strength) and subjective reports were collected during every waking trial of each session. *Results:* Total sleep time, and consequently, sleep efficiency, was statistically higher under zaleplon than under placebo (sleep efficiency = 87% and 76%, respectively). The majority of the gain in sleep occurred during sleep stages 3 and 4. Unexpectedly (given that the participants were well rested) a few of the cognitive performance and memory variables showed improvement after awakening under zaleplon when compared to placebo. *Conclusion:* Zaleplon, when used by rested individuals for daytime sleep, improves sleep quality.

15. SUBJECT TERMS
Fatigue, Sustained Operations, Daytime Sleep, Nap, Performance Enhancement, Zaleplon, Sleep Aids

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
					Jeff Whitmore
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
Unclass	Unclass	Unclass	Unclass	31	(210) 536-3595

ABSTRACT

Rationale: Zaleplon appears to be a prime candidate for assisting individuals in obtaining sleep in situations not conducive to rest. *Objectives:* The primary objective of this study was to determine whether zaleplon (10-mg) effectively promoted sleep during the daytime in well rested individuals when compared to placebo. A secondary objective was to see if, while not expected, the use of zaleplon impacted the performance of these well rested individuals upon awakening. *Methods:* Twelve participants, 6 males and 6 females, participated in this study. The study was conducted using a repeated measures design with two within-subject factors: drug (placebo/zaleplon) and trial (hourly testing during waking hours). Each participant experienced both drug conditions, with drug administration being counterbalanced and double-blinded. During a 3.5 hour nap following drug administration, polysomnographic variables were recorded to measure quality of sleep. Performance measures (cognition, memory, balance, and strength) and subjective reports were collected during every waking trial of each session. *Results:* Total sleep time, and consequently, sleep efficiency, was statistically higher under zaleplon than under placebo (sleep efficiency = 87% and 76%, respectively). The majority of the gain in sleep occurred during sleep stages 3 and 4. Unexpectedly (given that the participants were well rested) a few of the cognitive performance and memory variables showed improvement after awakening under zaleplon when compared to placebo. *Conclusion:* Zaleplon, when used by rested individuals for daytime sleep, improves sleep quality, and may have a positive impact on some cognitive and memory functions.

INTRODUCTION

In many instances, operational performance may be increased if operators were able to accomplish sleep during brief (<6 hrs) daytime break periods. Operational examples include individuals rotating schedules (i.e., preparing for an initial night shift), night work, and sustained work environments (i.e., military operations). It is difficult if not impossible to accomplish daytime sleep in many circumstances. This may be due to environmental factors (e.g., noise, light), subjective factors (e.g., anxiety), or circadian factors (e.g., reduced melatonin production). In these cases an effective short-acting sleep aid may provide a substantial improvement in the ability to acquire daytime sleep. The aid of choice should have a relatively short half-life and few side effects upon awakening from sleep. In addition, the sleep-aid should have minimal side effects when sleepers are awakened unexpectedly and required to return to work. Finally, the sleep-aid of choice should be effective at inducing and maintaining daytime sleep. As detailed in the following paragraphs, zaleplon (marketed in the United States by Wyeth-Ayerst Pharmaceuticals under the name Sonata®) may be a sleep aid that would fulfill these requirements.

Maximum plasma concentrations of zaleplon occur at approximately 1-hr post-dose with a half-life of about 1-hr (Beer, Ieni, Wu, Clody, Amorusi, Rose, Mant, Gaudreault, Cato, and Stern, 1994). Zaleplon is commonly administered in 10-mg oral doses, but is also given in 20-mg doses to people more resistant to its effects, for the treatment of insomnia. The most common side effects include: headache, dizziness and somnolence. Outside of somnolence, in short-term clinical studies, the subjective side effects for zaleplon are not significantly different from placebo following a night of sleep (Elie et al.). Thus, from a pharmacokinetic and symptomatic perspective it appears that zaleplon may be suited for situations where a rest break of at least 4-hours duration is available.

Zaleplon has been shown to reduce nighttime sleep latency in adult insomniacs at the 10-mg dose level (Elie, Ruther, Farr, Emilien, & Salinas, 1999). Hedner, Yaeche, Emilien, Farr, & Salinas (2000) showed an increase in subjective sleep quality and subjective total sleep time for nighttime sleep in elderly insomniacs. This group also found a reduction in subjective sleep latency for both 5 and 10-mg doses. Fry, Scharf, Mangano, & Fujimori (2000) found zaleplon to be an effective sleep aid (5, 10, & 20-mg) without withdrawal symptoms in outpatient insomniacs. Walsh, Vogel, Scharf, Erman, William, Schweitzer, Mangano, and Roth (2000) evaluated the hypnotic efficacy of 10-mg zaleplon and found a significant reduction in nighttime sleep latency (subjective and polysomnographic data). Total sleep length was not significantly increased. This 5-week study found no rebound insomnia upon zaleplon termination. In summary, there is significant evidence to support the hypnotic efficacy of zaleplon in insomniacs attempting to sleep at night. The question of whether there are benefits to normal rested individuals attempting daytime sleep remains.

Several studies have found little or no difference in performance following a night-time administration of zaleplon (Danjou, Paty, Fruncillo, Worthington, Unruh, Cevallos, & Martion, 1999; Hindmarch, Patat, Stanley, Paty & Rigney, 2001; Troy, Lucki, Unruh, Cevallos, Leister, Martin, Furlan, and Mangano, 2000). However, several other studies have discerned some negative performance effects (Vermeeren, Danjou, & O'Hanlon, 1998; Curran, & Lader, 1993, Beer et al., 1994). Only one study to date has found significant negative effects beyond three hours post-dose for a single dose of 10-mg zaleplon (Vermeeren et al.). In previous work (Whitmore, Fischer, Barton, & Storm, 2003), we explored zaleplon's deleterious effects upon performance following an unanticipated awakening from daytime sleep. This study found complex cognitive performance to be significantly affected up to 3-hrs post dose. However, simpler performance measures (i.e., simple reaction time, grip strength) were unaffected. The short duration of negative performance impact supports zaleplon usage in environments where only a brief period is available for sleep.

Our present study is somewhat different from those described in the preceding paragraphs. This study was designed to examine zaleplon's ability to improve both the quantity and quality of daytime sleep in a

normal, rested, adult population. Such a situation would represent a near-worst case scenario for testing the hypnotic efficacy of a substance. That is, we are attempting to induce sleep in rested individuals during a time of day when they would not normally sleep. In summary, the primary goal of this research was to evaluate zaleplon's hypnotic efficacy for daytime sleep in rested individuals. A secondary goal was to study the post-awakening performance impact of zaleplon in this scenario.

METHODS

Participants

Twelve participants, six males and six females, volunteered to participate in this study. The mean age of the group was 28.1 years (range 19 – 43 yrs). The mean weight for males was 78.65 kg. (range 63.50 – 89.36 kg) and the mean weight for females was 58.33 kg (range 44.45 – 70.31 kg). Based upon a participant demographic survey, participants were normally entrained individuals (i.e., no night-shift workers), who were not heavy caffeine users. Participants were screened medically (blood chemistry and liver function) prior to their first experimental session. The study required a total of 23 hours of time per individual. Participants were paid for their participation and signed a voluntary consent document prior to participation. Because of facility accommodation limitations, participants were formed into three groups of four participants each. Each group of participants experienced one experimental session per week (10-hours duration) for two successive weeks. In addition a 3-hour training session was conducted the week prior to the first experimental session. The research protocol for this experiment was reviewed by the Brooks Air Force Base Institutional Review Board and approved by the Air Force Surgeon General (#F-BR-2002-0030-H). All funding for this effort came from the Air Force Research Laboratory through contract #F41624-97-D-6004.

Design

The study was conducted using a repeated measures design with two within-subject factors: drug (zaleplon or placebo), and trial (six data collection time points; Table 1). Each participant experienced both drug conditions. The two experimental sessions were separated by one week. Drug administration was counterbalanced and double-blinded. Participants were asked not to consume alcohol the night before an experimental session, and to drink no more than one caffeinated beverage on the morning of an experimental session. They were told to get a good (normal) night's sleep the night before each session.

Time	Activity
1030	Arrive - Practice
1100	lunch
1200	Test-Baseline
1300	Dose / Sleep
1630	Awaken / Test 3.5-hrs
1700	Test 4-hrs, WM
1800	Test 5-hrs
1900	Test 6-hrs, WM
2000	Test 7-hrs – dinner
2100	Session Complete
TEST = ANAM, PVT, POMS, Symptom Survey, Force Platform and Grip Strength WM = Word Memory	

Table 1 Experimental session schedule.

Facility and Materials

The study was conducted at the Chronobiology and Sleep Laboratory (CASL) located at Brooks Air Force Base. Each participant was assigned a number under which his or her data was recorded to maintain anonymity. The lab layout consisted of four bedrooms and bathrooms, and one additional room containing equipment for measuring postural sway. Participants completed cognitive tasks at computer workstations within their bedrooms. The workstations were located next to the beds so that participants could sit down at their desks immediately upon waking. Participants completed all cognitive tasks with their bedroom door closed to limit distractions. Audio-visual equipment was used to monitor the testing areas for safety purposes.

The zaleplon doses used in this study were 10-mg Sonata® capsules obtained in an unopened manufacturers bottle. These capsules were individually re-packaged inside a gelatin capsule. Gelatin

capsules of identical appearance, but containing granular fiber, were constructed as the placebos. The capsules were prepared and randomized by the pharmacy at Wilford Hall Medical Center, Lackland AFB, TX.

Tests and Measures

ANAM – A selection of tests from the Automated Neuropsychological Assessment Metrics, a cognitive performance assessment battery (Perez, Masline, Ramsey, & Urban, 1987), was administered at each of the six test trials (see Table 1), each test day. The entire ANAM test battery took 13 to 15 minutes to complete. All tests are listed below in the order of presentation. Table 2 shows the individual test start times and durations during the first test block after awakening.

Stanford Sleepiness Scale (SSS) – Participants chose one of seven Likert-scale descriptors, ranging from 1, "Feeling active and vital; alert; wide awake," to 7, "Almost in reverie; sleep onset soon; lost struggle to remain awake." (Hoddes, Zarcone, Smythe, Phillips, & Dement, 1973)

Code Substitution Learning Test – This test provided a reference row with pairs of numbers and associated symbols at the top of the screen. During the test, individual stimulus items containing one pair, number and symbol, were presented below the reference row. Participants used the reference row to determine whether or not a number and symbol were associated with each other. A total of 72 items were presented during this test.

Code Substitution Immediate Memory Test – This test presented 18 number and symbol items, without providing the reference row of numbers and symbols. Participants were to recall the Learning Test associations to make their determination.

Simple Reaction Time Test (SRT) – This test required participants to respond as quickly as possible with a mouse click to an asterisk stimulus appearing on the screen. A total of 20 stimuli were presented.

Mathematical Processing Test – This test called for participants to perform addition and subtraction problems by responding to whether or not the answer was greater or less than 5 with the answer never being 5. Each problem consisted of three single-digit numbers and two operands. The test lasted for 3 minutes.

Matching to Sample Test – This test displayed a sample matrix box containing a pattern of red and blue squares. After the sample matrix was presented, it was replaced with two matrix boxes. Participants had to decide which of the two matrix boxes matched the sample stimulus using a left or right mouse click. The test lasted for 3 minutes.

Symbolic Logical Reasoning Test – In this test, participants answered whether a single statement accurately described the relational order of two symbols (# and &). The test lasted 3 minutes.

Code Substitution Delayed Memory Test – This test was similar to the Immediate Memory Test, but contained 36 items. Again, participants had to respond to whether the number and symbol stimulus were associated based upon the reference row provided only during the Code Substitution Learning Test.

In general, for these ANAM tests, the following outcome measures were recorded for analysis: accuracy, mean reaction time to correct responses (MRTC), standard deviation of

reaction time to correct responses (SDRTC), throughput (($60,000/RT_{All}$) * % Correct), and omissions. The exceptions to this rule were the SSS (a single sleepiness rating from 1 to 7 was recorded), and SRT (only mean reaction time, percent omissions, and standard deviation for reaction time were examined).

Word Memory Test – This test provided an assessment of short-term memory. In this study it was used to test for anterograde amnesia effects. Approximately 30 minutes after awakening, the participants were aurally presented a 15-word list. They wrote down the words on a piece of paper. The word lists were selected from the Williams Word Memory Test (Williams & Williams, 1966). After a one-minute memorization period, participants handed in their papers. Fifteen minutes later they were asked to recall the list on paper. After an additional three hours, participants were asked once more to recall and write down as much of the list as possible. The number correct was the single outcome measure derived from this test.

Test Start Time (min)	Test Duration*	Activity
0	.5	Stanford Sleepiness Scale
.5	1.5	Code Substitution - Learning
2.0	.5	Code Substitution - Immediate
2.5	.5	Simple Reaction Time
3.0	3.0	Math Processing
6.0	3.0	Matching to Sample
9.0	3.0	Logical Reasoning
12.0	1.0	Code Substitution – Delayed
13.0	1.5	Word Memory Memorization
14.5	10.0	Psychomotor Vigilance Test
24.5	2.0	Profile of Moods States
26.5	1.5	Grip Strength
28.0	2.5	Force Platform
30.5	1.0	Word Memory Recall
* includes transition times between tests		

Table 2 Test order and duration upon awakening.

Psychomotor Vigilance Task – The PVT required sustained attention and discrete motor responses (Dinges, 1992). The 8" x 4.5" x 2.4" portable, battery-operated device presented a continuous simple reaction time test for 10-minutes. Training required only one ten-minute practice session. The PVT was self-administered at all trials. The outcome measures from this test were mean reciprocal reaction time (MRRT), standard deviation of RRT (SDRRT), and number of lapses. RRT was used here instead of RT because of the nature of the PVT, which tends to exacerbate the usual problems with RT data (e.g. skewness).

Profile of Mood States (POMS) – This paper-and-pencil survey was used to assess affect (McNair, Lorr, & Droppleman, 1971). The POMS consisted of sixty-five adjectives describing feeling and mood to which the participant responded according to a five-point scale ranging from "Not at all" to "Extremely." There were six subscales derived from the questions: Depression, Tension, Vigor, Fatigue, Anger and Confusion. The POMS was administered at all trials.

Sleep Aid Symptom Questionnaire - To assess sleep aid subjective effects, participants were asked to complete a symptom survey containing 56 items, each scored on a scale ranging from 0-7, where 0 was "none" and 7 was "severe". Participants were to note whether or not they thought that the drug administration caused the symptom and also to what extent they thought the symptom would interfere with daily activities. Of the 56 symptoms, 17 were considered to be relevant to this study, and only those were analyzed. The questionnaire also called for participants to indicate whether or not they thought they received the placebo or Sonata. Participants completed this questionnaire every trial.

Grip Strength – Strength was assessed with a Sammons Preston JAMAR hand dynamometer (Hamilton, Balnave, & Adams, 1994) five times each test day. Each of the five trials consisted of two 5-sec squeezes that were separated by one minute's rest. Two values were recorded for each trial of which the highest was used as the outcome measure for this test.

Force Platform Test – Postural stability was assessed by requiring the participant to stand upon a platform that measures changes in the body's center of pressure over time (Platform model OR6-5-1, strain-gage amplifier model SGA6-4, a-to-d converter model DT2801; AMTI, Watertown MA). This test had been used previously to analyze postural stability after benzodiazepine administration (Patat & Foulhoux, 1985). The participants' posture was heels together, feet open at a 30-deg angle, and hands at sides, much like a relaxed version of the military position of attention. One minute of data was collected for both eyes open and eyes closed conditions, at a sampling rate of 10 Hz. The Force Platform Test was completed every trial. An area measurement that accounted for 95% (A95) of the variation in the center of pressure changes was used as the outcome measure.

Polysomnography – Sleep onset and quality during the experiment were assessed with ambulatory electrophysiological equipment. Brain electrical signals were acquired from the O4, C2, A1 and A2 scalp leads of the International 10-20 system (Jasper, 1958) with an EEG Technology ambulatory recorder (model #34-24R8B20, Leveroy, Netherlands) and analyzed with software developed by Stellate Systems (Montreal, Canada). The EEG signal was digitized at 128 samples/sec. EOG signals were also acquired to support sleep scoring by a polysomnographic technologist. In total, ten electrodes were used (3 scalp, 2 mastoid, 2 outer canthi, 2 chin, 1 forehead). Participants wore the electrodes for a total of four hours each session. Sleep latency, total sleep time, time spent in each stage of sleep, and stage of sleep upon awakening were assessed.

Actigraphs - SleepWatch-L model actigraphs were issued to each participant (Ambulatory Monitoring, Inc., Ardsley, NY). The actigraph resembles a wristwatch and was worn in a similar manner. A small accelerometer systematically recorded the individual's movement over time, both while awake and asleep, allowing for the objective identification of sleep/wake patterns (Brown, Smolensky, D'Alonzo, & Redman, 1990). Each participant wore an actigraph for three days prior to each test day. Actigraphy was used to confirm activity log results.

Activity Log – Participants recorded their sleep intervals as they occurred for three days prior to each experimental session using a modified version of the form developed by the Air Force Research Laboratory (Cantrell & Hartman, 1967). This form allowed us to assess the number of hours slept each night for the three days prior to each session. Subjective rating scales were also provided to periodically register sleepiness ratings.

Procedures

A training session was conducted the week prior to data collection. During training, participants completed 6 trials of the ANAM battery to assure asymptotic performance on each test. Training on the other tests required only a single trial, and was conducted on the morning of the first experimental session. At the conclusion of the training session, participants were given actigraphs and activity logs for the first test week.

For each experimental session, participants arrived at 1030 hrs and completed one ANAM training test trial to become re-familiarized with the tests. Participants were also introduced to the remaining tests at that time. Lunch was served after these familiarization trials. EEG electrodes were then installed and data recording begun. Prior to sleep, participants completed their first testing trial at 1200 hrs (baseline). Drug administration occurred at 1300 hrs and participants slept from 1300 to 1630 hrs. Participants were awakened at 1630 hrs and were told to remain in bed until a proctor

could help them into their chairs at the computer workstations. Testing began once everyone was seated (1630 hrs, which is 3.5-hr post-dose). Testing was performed again at 1700 hrs, and was repeated hourly through 2000 hrs. Participants were given half hour breaks each hour. At the conclusion of the first test day, participants were given actigraphs and activity logs for the next test week. Participants returned the following week for the second experimental session.

Statistical Analyses

Drug Comparisons

Before any statistical analyses were performed, the data was baseline-adjusted to counter any potential week-to-week differences in an individual's responses. This was accomplished for each outcome measure (except Williams word memory and PSG responses, which did not have baselines) by subtracting a subject's baseline response from each of his post-drug responses. These "deltas" became the data for statistical analysis.

For each continuous, normally distributed, outcome measure, a repeated measures analysis of variance was performed (using the delta data) to test for significant drug main effects and/or drug by time interaction. A Huyhn-Feldt adjustment was made for variables that failed Mauchly's Test of Sphericity. When significant drug effects were detected, post-hoc simple effects tests (Winer, pg. 174) were used to compare the zaleplon change from baseline with the placebo change from baseline at each post-drug time point, separately. For discrete outcome measures, and measures where non-normality was suspected, Wilcoxon signed-rank tests were used to compare the drug and placebo conditions for differences in the change from baseline at each of the post-dose trials, separately. Finally, for polysomnographic variables, Student's one-tailed paired t-tests were used to compare the effects of zaleplon with placebo.

Sleep Inertia

Only data from the first four trials (baseline, 3.5-hr post-dose, 4-hr post-dose, 5-hr post-dose) of the placebo condition were examined to determine sleep inertia effects. The analysis was restricted to the placebo data to insure that any changes seen would be due to a simple sleep inertia effect, and would not be compounded by a possible zaleplon carryover. A repeated measures ANOVA with one within-subjects factor (time) was performed on each dependent measure. When a significant effect was observed, post-hoc comparisons between baseline and each of the post-awakening time periods were performed using Student's t-tests.

Power Analysis

The number of subjects for this study was calculated from an a priori power analysis of the planned post-hoc comparisons between the two drug conditions. We determined that, when testing at the 0.05 alpha level, a sample of 12 participants would provide an 88% chance (power) of detecting a standardized effect size (ES) = 1.0 when comparing the change under zaleplon with the change under placebo at any given time point.

RESULTS

One of the twelve participants was dropped from the study due to the development of a medical concern unrelated to the study. An additional participant was removed from the polysomnographic analysis due to data loss in for one experimental session. The results will be discussed in two sections. The first section details the outcomes of the drug comparisons. The second section examines only the placebo data for sleep inertia effects. Any mention of statistical significance refers to an alpha level of .05.

Zaleplon vs. Placebo Comparisons

For all variables that were recorded over the hourly trials, descriptive statistics are shown in Appendix A, along with the analysis results. The first column contains the actual baseline (pre drug) means as a point of reference. The remaining columns contain the mean changes from baseline, which were the means being compared in the statistical analyses. Descriptive statistics and results for the polysomnography variables are shown in Appendix B. Results for any other variables are summarized in the text. Graphs are presented for all variables showing significant effects. In the graphs, for ease of interpretation, the means, rather than the mean deltas are shown. For variables where non-parametric tests were performed, means were used in both the tables and the graphs to provide trend information even though the analyses were based on the ranked data. Note that the 3.5-hr post-dose trial is the trial performed immediately upon awakening, and contains data from 3.5-4 hrs post-dose. Similarly, the other post-dose trials began at the time indicated post-dose and had a duration of 25-40 min.

Sleep and Activity

Based on data collected with the activity logs, there was no difference between the average sleep attained preceding the zaleplon and placebo sessions. Overall, participants averaged 6.8 hours of sleep the night prior to an experimental session. The mean sleep start time was 23:54.

Polysomnography

See Appendix B for details of the analyses performed on the polysomnographic variables. Mean total sleep time (TST) was significantly longer under zaleplon compared to placebo (182 min vs. 163 min). Consequently, sleep efficiency was also significantly higher during the zaleplon session (87% vs. 76%). Total slow wave sleep (TSWS = stage 3 + stage 4 sleep) was significantly greater for the zaleplon condition (54.0 vs. 37.4 min). Split into Stages 3 and 4, separately, we observed a significant gain in stage 3 sleep under zaleplon (60% increase over placebo), and a borderline-significant ($p<.10$) gain in stage 4 sleep under zaleplon (37% increase over placebo). To aid with interpretation of the analysis results for TST and TSWS, individual subject responses are shown in Figures 1 and 2. Note that four subjects (those with the lowest placebo TST) experienced large increases in TST under the zaleplon condition (ranging from 21% to 74% improvement), whereas the six subjects whose placebo TST's were already high, experienced moderate to little improvement under zaleplon (in fact, 3 did not accomplish as much sleep under zaleplon). Thus we observed, for zaleplon, that the TST range and standard deviation are greatly reduced when compared to placebo. Similar results were seen for TSWS: Five of the six subjects with the lowest placebo TSWS showed very large increases under zaleplon ranging from 86% to 148% improvement (the sixth showed only slight improvement), whereas the four subjects whose placebo TSWS's were already high experienced little improvement under zaleplon (two did not accomplish as much TSWS under zaleplon). Finally, note that every subject showed improvement under zaleplon in at least one of the two measures (TST or TSWS).

The results for the remaining polysomnographic measures were less remarkable. The times spent in stages 1, 2, and REM were nearly identical for the zaleplon and placebo sessions. There was no significant difference found for sleep latency. Stage of sleep upon awakening also did not differ between conditions. Participants were generally awakened from either REM or Stage-II sleep under placebo and either Stage-I or Stage-II under zaleplon.

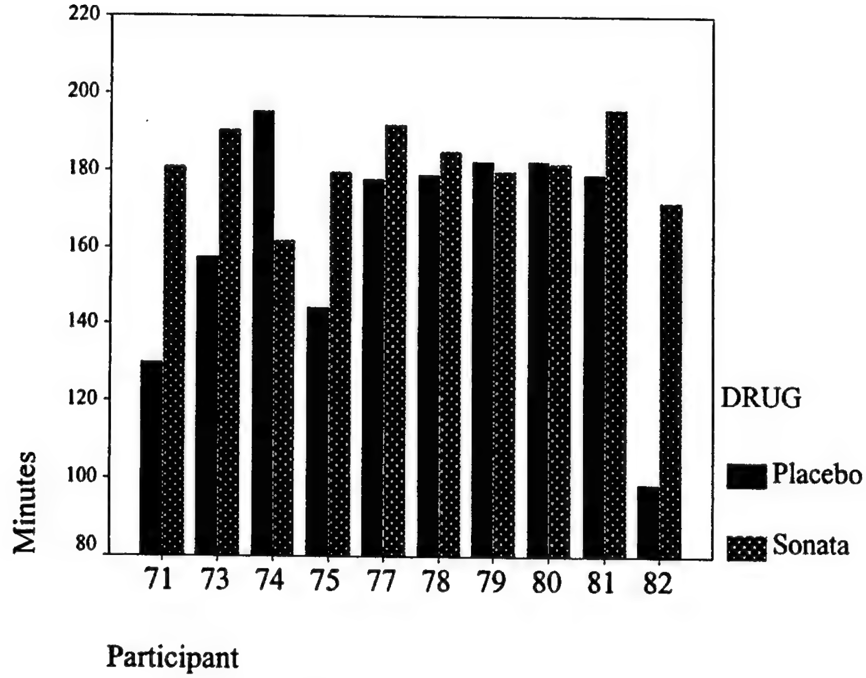


Figure 1: Total Sleep Time

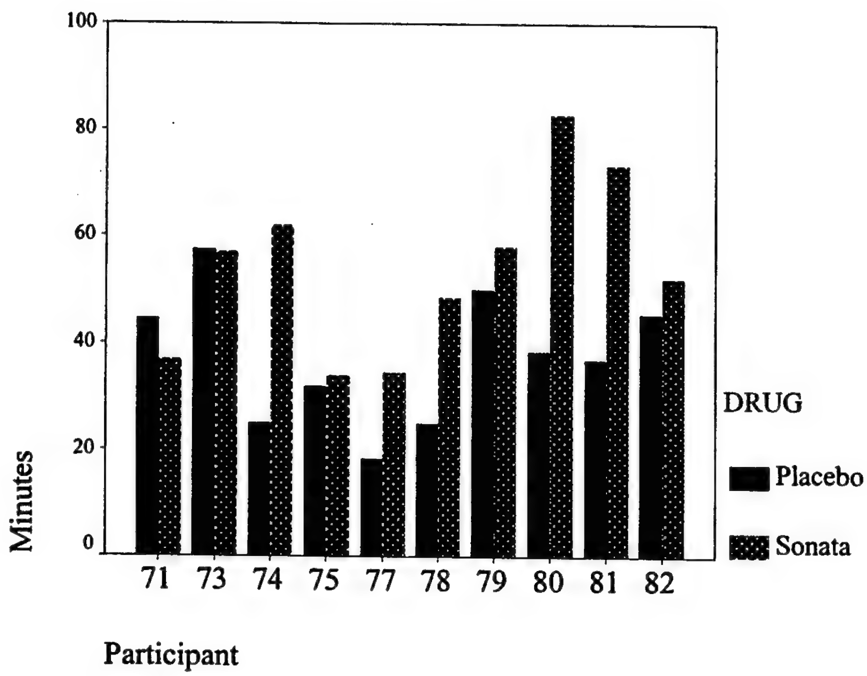


Figure 2: Total Slow Wave Sleep

Cognitive Performance and Memory

Code Substitution Test-Learning– A significant drug by trial interaction was detected for MRTC, and a significant drug main effect was detected for throughput. Under zaleplon, MRTC significantly decreased from baseline at both the 4-hr (t(10)=2.67, P=.023) and 7-hr (t(10)=2.95, P=.015) post-dose

trial when compared to placebo (see Fig 3). Under zaleplon, throughput significantly increased from baseline values at both the 4-hr (t(10)=2.83, P=.018) and 7-hr (t(10)=2.80, P=.019) post-dose trials when compared to placebo (see Fig 4).

Code Substitution Test-Immediate– No significant drug effects were seen for any of the five outcome measures.

Code Substitution Test-Delayed– No significant drug effects were seen for any of the five outcome measures.

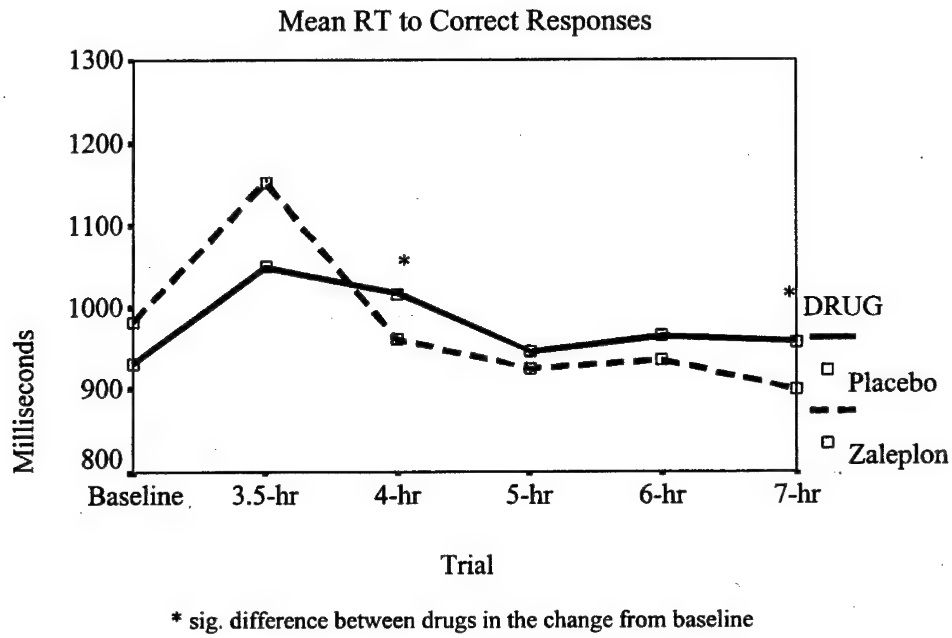
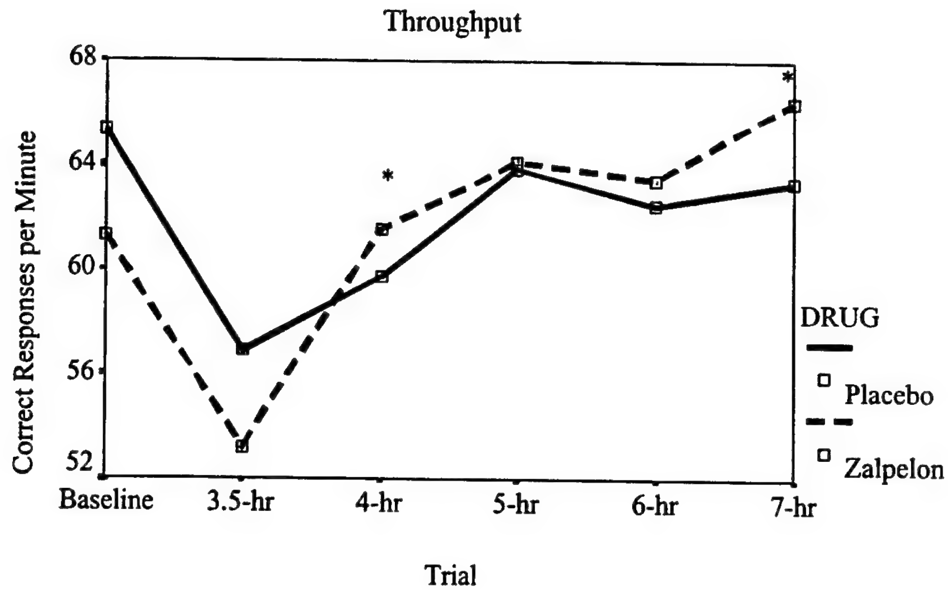


Figure 3 Code Substitution Test-Learning



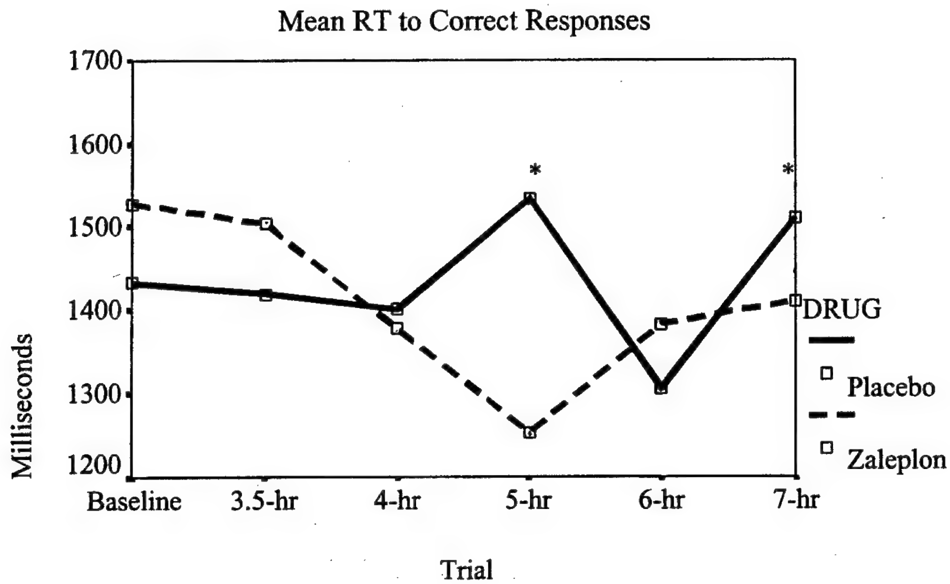
* sig. difference between drugs in the change from baseline

Figure 4 Code Substitution Test-Learning

Math Processing Test– A significant drug by trial interaction was detected for accuracy. However, from the post-hoc tests, no significant difference was found between placebo and zaleplon at any specific trial. No statistical differences were found for any of the other four outcome measures.

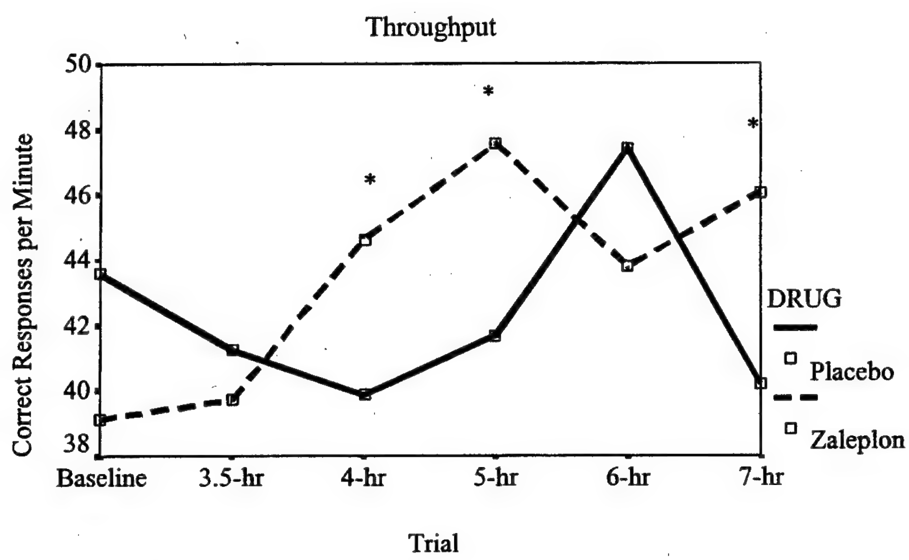
Logical Reasoning Test– No significant drug effects were seen for any of the five outcome measures.

Match to Sample Test– Significant drug main effect differences were detected for MRTC and throughput. Under zaleplon, MRTC significantly decreased from baseline at both the 5-hr ($t(10)=2.97$, $P=.014$) and 7-hr ($t(10)=3.70$, $P=.004$) post-dose trial when compared to placebo (see Fig 5). Under zaleplon, throughput significantly increased from baseline values at the 4-hr ($t(10)=3.84$, $P=.003$), 5-hr ($t(10)=2.69$, $P=.023$) and 7-hr ($t(10)=4.64$, $P<.001$) post-dose trials when compared to placebo (see Fig 6).



* sig. difference between drugs in the change from baseline

Figure 5 Matching to Sample



* sig. difference between drugs in the change from baseline

Figure 6 Matching to Sample

Simple Reaction Time Test– No significant drug effects were seen for any of the three outcome measures.

Psychomotor Vigilance Test– No significant drug effects were seen for any of the three outcome measures.

Williams Word Memory Test--There was no within-session baseline for this test. Consequently, evaluations were made by comparing the percent correct between placebo and zaleplon at each time point, separately. Given the discrete nature of the data a Wilcoxon Signed Rank Test was utilized. Word recall was significantly higher under zaleplon than under placebo ($z=2.22$, $p=.026$) at the 7-hr post-dose trial (see Fig 7).

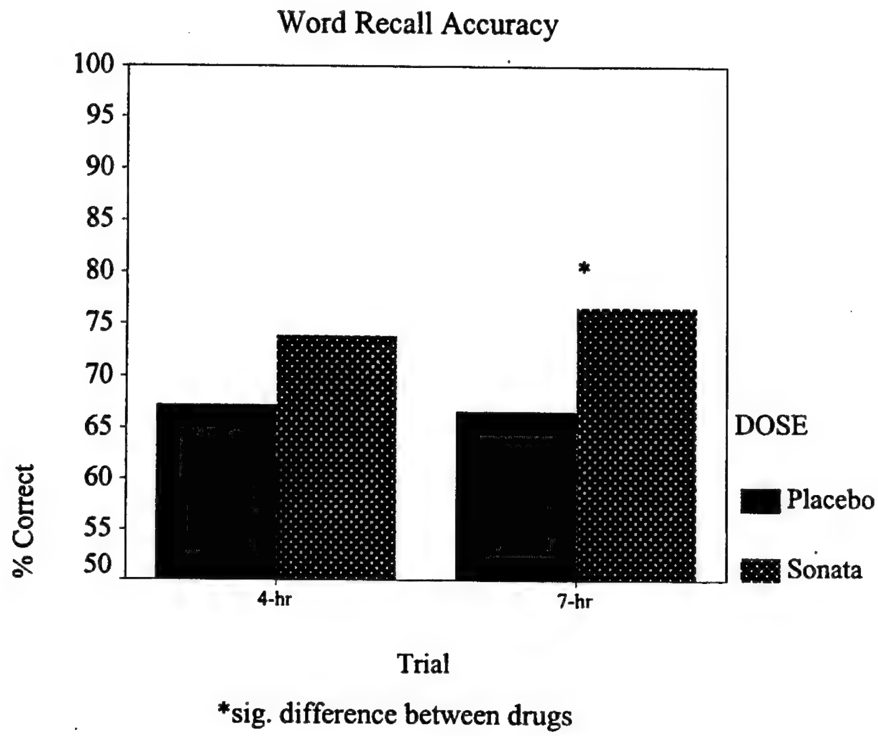


Figure 7 Word Memory Recall Performance

Balance & Strength

Force Platform Test– Separate analyses were performed for the eyes open and eyes closed conditions. No significant drug effects were seen under either condition for the A95 outcome measure.

Grip Strength- No significant drug effects were detected for max grip strength.

Subjective Data

Sleepiness Rating- No significant difference was found between zaleplon and placebo with respect to sleepiness scores.

Profile of Mood States- No significant drug effect was seen for any of the six POMS subscales.

Sleep-Aid Symptoms Questionnaire- To prepare for significance testing, difference scores indicating the change from baseline to each of the post-awakening trials were calculated. A Wilcoxon signed-rank test was then performed comparing the drug conditions. No significant differences were found between the drug conditions for any of the 17 variables analyzed. (See Appendix C for symptom summary values) Following awakening in the second experimental session, participants were asked to identify which drug they received. Forty five percent of the participants (5 out of 11) guessed the dose accurately.

Sleep Inertia Results

As indicated in "methods", only the first four placebo trials were analyzed for sleep inertia effects. The ANOVA results are summarized in Appendix D for all variables analyzed. The means that were tested are the same as were previously shown in Appendix B. Figures are provided for all variables where significant sleep inertia was found.

Code Substitution Test-Learning–Significant trial main effects were detected for MRTC and throughput. MRTC significantly increased at the 3.5-hr ($t(10)=3.22$, $p=.009$) post-dose trial when compared to baseline (see Fig 8). Throughput significantly decreased at the 3.5-hr ($t(10)=3.86$, $p=.003$) and 4-hr ($t(10)=2.26$, $p=.048$) post-dose trials (see Fig 9).

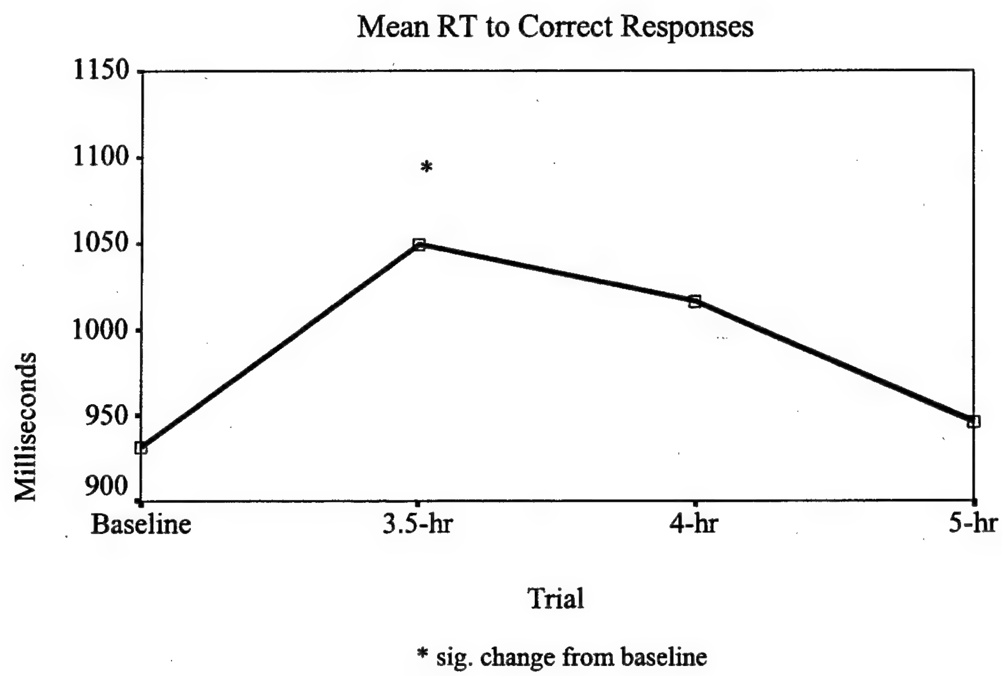


Figure 8 Code Substitution Test-Learning

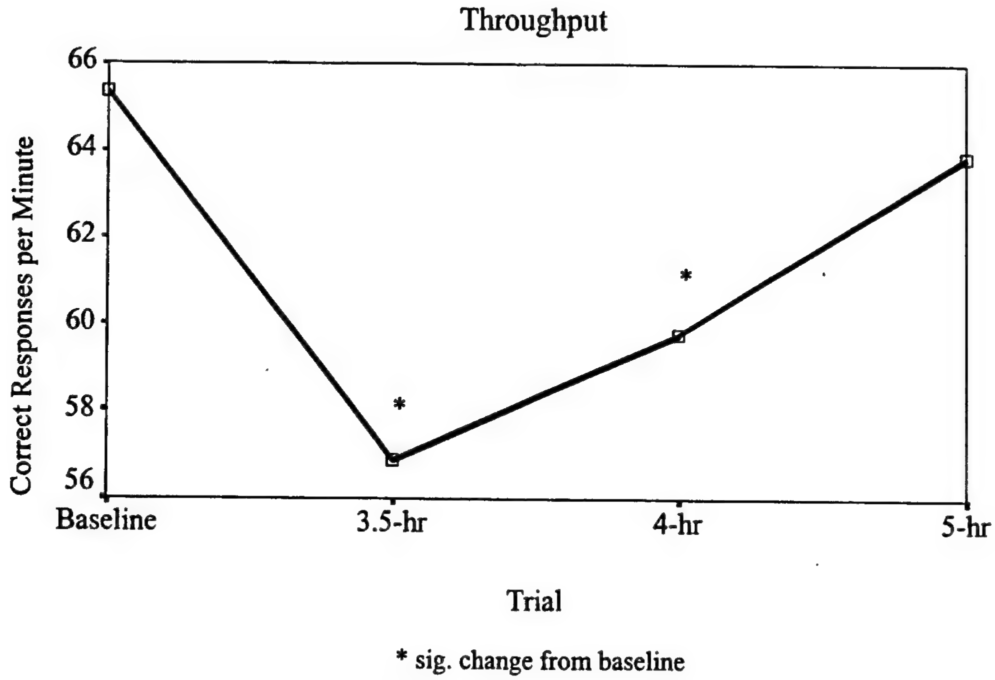


Figure 9 Code Substitution Test-Learning

Code Substitution Test-Immediate– A significant trial main effect was detected for throughput (see Fig 10). Throughput significantly decreased at the 3.5-hr ($t(10)=2.25$, $p=.048$) post-dose trial when compared to baseline.

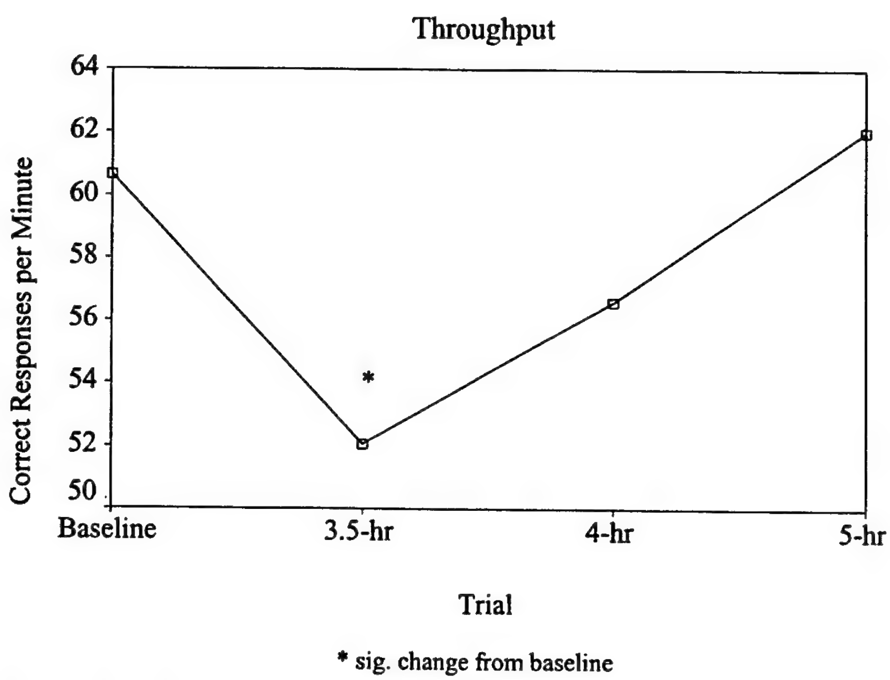


Figure 10 Code Substitution Test-Immediate

Code Substitution Test-Delayed– No significant trial main effects were detected for any of the four outcome measures.

Math Processing Test- No significant trial main effects were detected for any of the four outcome measures.

Logical Reasoning Test– Significant trial main effects were detected for MRTC and throughput. Post-hoc comparisons indicated increased MRTC ($t(10)=3.14$, $p=.010$) and decreased throughput ($t(10)=3.31$, $p=.008$) at the 3.5-hr post-dose trial, when compared to baseline (Fig.s 11 & 12, respectively).

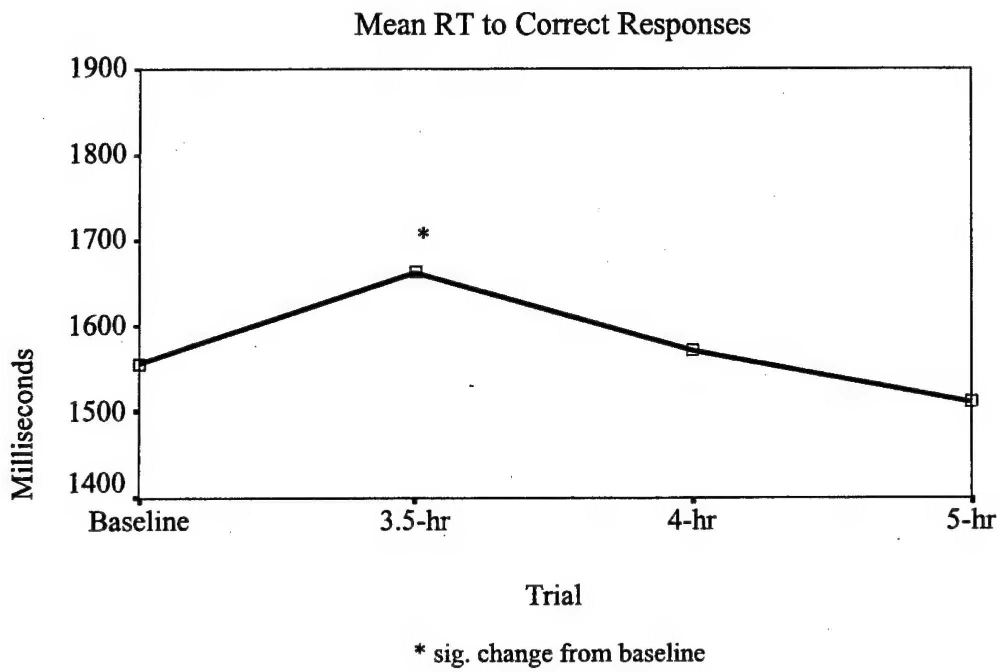


Figure 11 Logical Reasoning Test

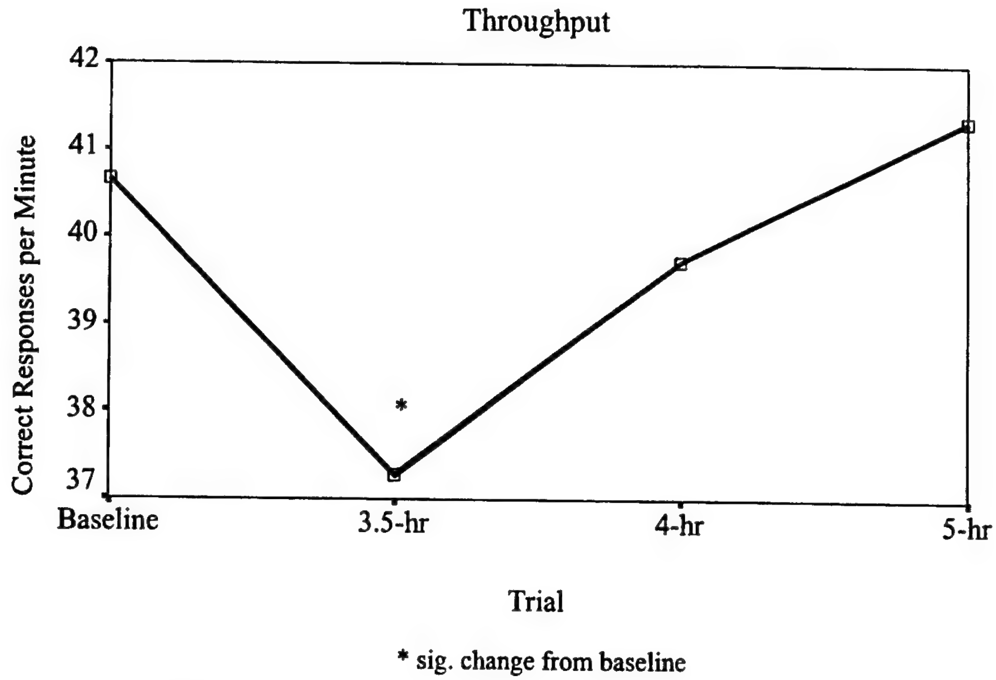


Figure 12 Logical Reasoning Test

Match to Sample Test– No significant trial main effects were detected for any of the four outcome measures.

Simple Reaction Time Test– A significant trial main effect was detected for MRT. Post-hoc comparisons indicated increased MRT at the 3.5-hr ($t(10)=3.72.$, $p=.004$) post-hoc trial when compared to baseline (Fig 13).

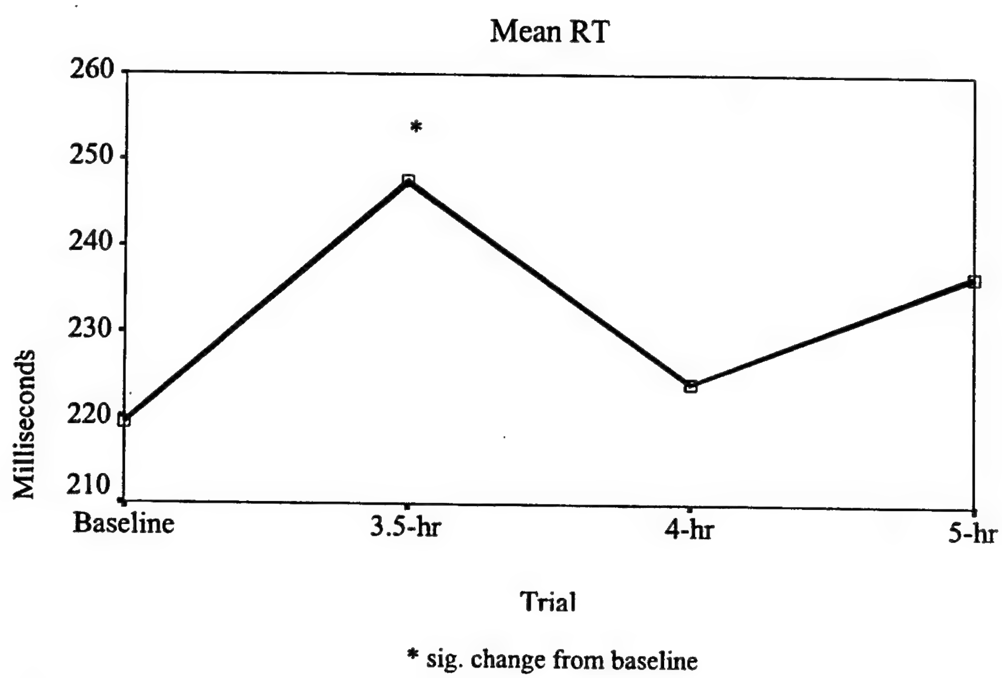


Figure 13 Simple Reaction Time

Psychomotor Vigilance Test- A significant trial main effect was detected for MRRT and lapses. No post-hoc comparisons were significant for MRRT (Fig. 14). Post-hoc comparisons indicated a decrease in lapses at the 4-hr (z=2.06, p=.039) post-dose trial, when compared to baseline (Fig 15).

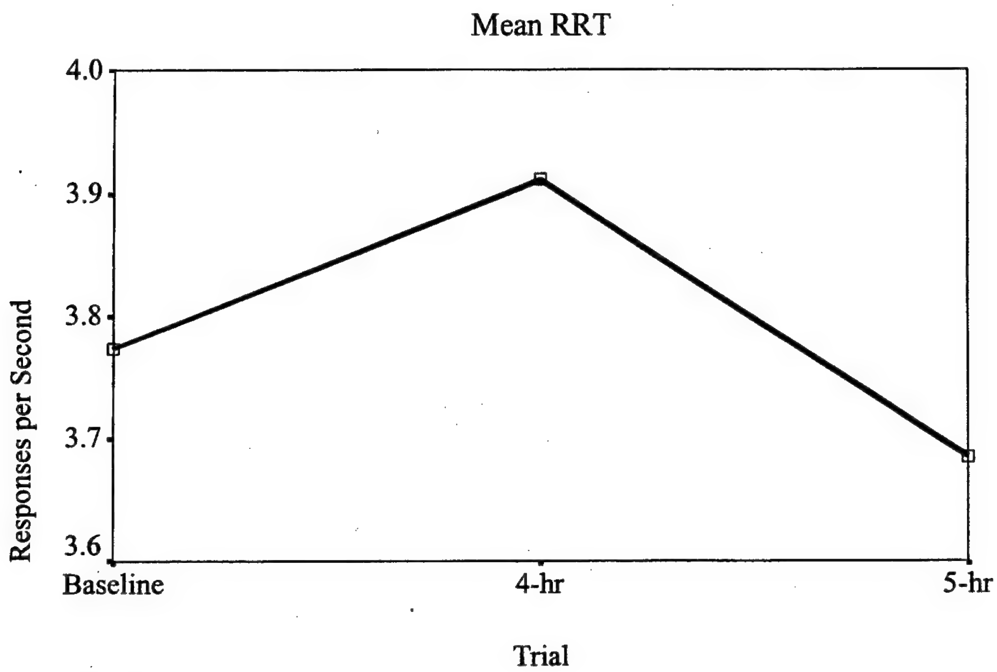


Figure 14 PVT

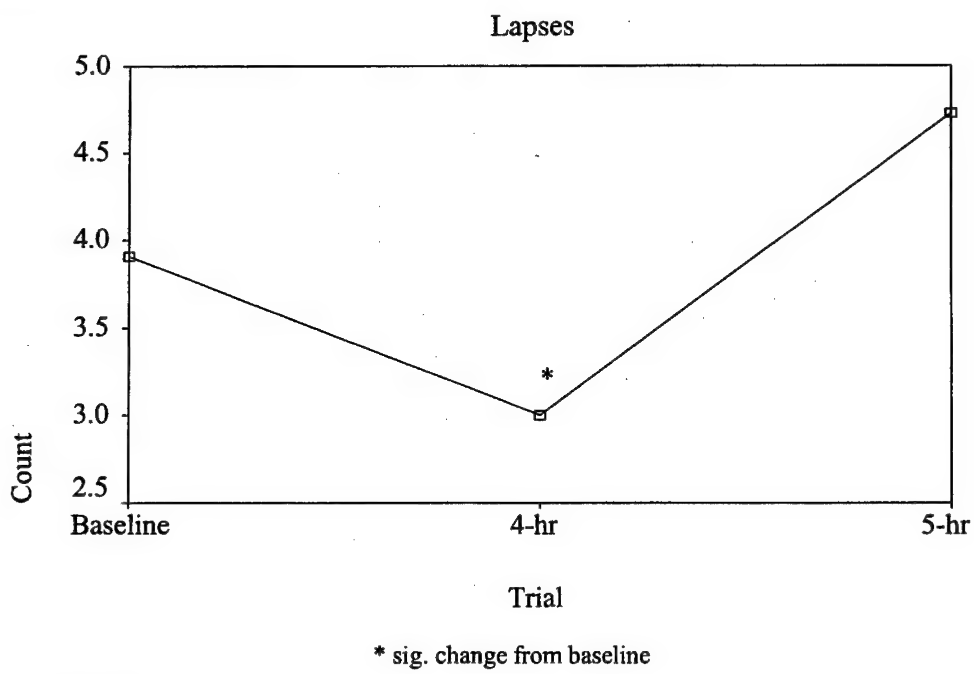


Figure 15 PVT

DISCUSSION

Zaleplon vs. Placebo

It is important to remember that the results from this study come from a group of normally entrained individuals who were attempting to sleep during a period when they would normally be awake. The sleep initiation start time was also a time where the propensity to remain asleep is low relative to nighttime levels in unrested individuals (Akerstedt, A. & Gillberg, M., 1981). Activity log data indicated that participants received what they would consider a normal nights sleep, not quite 7 hrs, prior to the experimental sessions. Thus, while not optimally rested, participants should have been relatively well-rested. This presents somewhat of a worst-case scenario for sleeping (i.e., a period where the drive for sleep should be greatly reduced relative to nighttime levels). In sum, we have sleep being attempted during a moderately fatiguing portion of the day by moderately well-rested individuals. Participants were able to sleep for a substantial duration, 2.72 hrs, under placebo. Thus it is quite a robust result that zaleplon significantly extended sleep duration (3.03 hrs) in this situation.

As noted in the results section, four participants responded very positively to zaleplon, five neutrally, and one negatively, in terms of sleep duration. Differences at the individual level could be attributable to a number of phenomena including sleep history or general stress level. Also worth noting is that the six participants unaided by zaleplon all slept around 180 minutes or greater under placebo. The potential benefits of zaleplon for accomplishing sleep three or more hours after ingestion are probably greatly reduced given its short half-life. The reduced range and standard deviation in TST under zaleplon indicate that the drug was stabilizing sleep duration across the group by removing the shorter sleep periods (i.e., the four shortest sleep periods occurred in the placebo group).

Overall, zaleplon improves both the duration and quality of sleep (i.e., amount of slow wave sleep) for the group. Upon examining the data at the individual participant level we observed a considerable improvement in either TST or TSWS, without a decrement in the other, in 7 out of 10 cases. In two cases under zaleplon (participant 71 & 74), we saw a decrease in either TST or TSWS with an increase in the other relative to placebo. In one case there was a considerable increase in both TST and TSWS (participant 81). Typically then (8 out of 10), participants were aided in their sleep by accomplishing more or better sleep.

There was no drug condition difference observed for sleep latency. Both groups fell asleep quickly (<14 min). Given this short placebo sleep latency, it is unlikely significant levels of zaleplon were in the participants system since the digestion time of the Sonata® capsule within a gel-cap should be approximately that duration or longer. This is in agreement with Mean Sleep Latency Test results from Richardson, Carskadon, Orav & Dement (1982) where they found participants to have a mean latency to sleep onset of approximately 12-min at 1330hrs. It must be remembered that sleep in this study was accomplished in a light and sound attenuating private room that was slightly cool (70° F). Participants were completely prone, resting upon a comfortable bed with a desired level of sheets and blankets. In other words, the sleep in this study was accomplished under ideal conditions; a situation which may or may not be present in an operational setting. Furthermore participants in this study were precluded from performing any other activities besides sleeping or reading in bed. This forced restriction of activity may well be a principal reason for the accomplishment of the great quantity of sleep observed under the placebo condition.

No deleterious performance effects, cognition, memory, balance or muscular, were observed under zaleplon, when compared to the placebo condition. To the contrary, cognitive performance, as measured by our battery of tests, was significantly improved in several cases for the zaleplon group relative to placebo. Keep in mind that both groups acquired a good deal of sleep. It must be

remarked as well that these improved performances occurred at times of day when performance is expected to be at its peak regardless of daytime napping. This improvement in performance was not overwhelming. There were a total of 36 cognitive and memory performance measures taken every trial. We observed improvement in a total of six variables at differing times following awakening. To attempt to determine if there was some facet of sleep that led to improved performance in this study, we examined the relationship between TST and TSWS and some performance variables which exhibited the greatest improvement under zaleplon relative to placebo (e.g., matching to sample throughput). No correlation between performance and either TSWS or TST, using either difference scores or group means, was observed. Thus, there is no clear explanation for the possibly beneficial results of zaleplon

Participants were unable to accurately determine whether they had received zaleplon or placebo. Additionally, no significant differences were observed for any of the symptom data. Nor were there any anecdotal reports of discomfort or unease following awakening from zaleplon-induced sleep. Thus participants awakened from a restful sleep not knowing whether they had received a sleep aid or not. This bodes well for post-awakening performance and supports zaleplon use in situations where only short periods are available for sleep.

This research shows zaleplon to be efficacious at promoting sleep in normal individuals during the day. It also shows that zaleplon increased the amount of slow wave sleep. However, as mentioned earlier, these results were observed in an environment ideal for sleep. Further research should investigate the robustness of the hypnotic efficacy of zaleplon by requiring individuals to sleep in less-ideal environments. In a study designed specifically to examine the sleep promoting effects of zaleplon in a non-conducive sleeping environment, Stone (2001) found zaleplon to reduce the time to persistent sleep over placebo.

In summary, zaleplon allowed participants to accomplish a greater amount of sleep and to sleep 'more deeply' than under placebo. Furthermore, performance was not adversely impacted following a 3.5 hour daytime sleep under zaleplon. On the contrary, there was the suggestion of improved cognitive performance in several instances. Thus zaleplon has shown significant benefits for individuals attempting to accomplish uninterrupted sleep during a non-optimal rest period.

Sleep Inertia

Four ANAM tests out of the seven had measures that showed a performance decrement at the 3.5hr test block. Three of the affected tests occurred within the first 3-minutes after awakening. The fourth affected test, Logical Reasoning, took place from 9 to 12 minutes following awakening. One measure from one test was negatively affected at the 4-hr test block. However, one measure from another test was significantly improved at the 4-hr test block. Thus it appears that there is substantial evidence for sleep inertia occurring up to 12-min following awakening but not thereafter. Half of the participants were awakened from Stage II sleep. The remainder were in REM (n=3), Stage IV(n=1), or very recently self-awakened (n=1).

CONCLUSIONS AND RECOMMENDATIONS

Zaleplon demonstrated significant benefits for individuals attempting to accomplish uninterrupted sleep during a non-optimal rest period. Zaleplon was capable of providing significant sleep enhancement during the day in relatively well-rested individuals. With normal use, zaleplon does not have a deleterious effect upon performance. Indeed performance may be enhanced following a normal awakening from sleep induced by zaleplon.

REFERENCES

Akerstedt, T., & Gillberg, M. (1981). The circadian variation of experimentally displace sleep. Sleep, 4, 159-169.

Allen, D., Curran, H., & Lader, M. (1993). The effects of single doses of CL 284,846, lorazepam, and placebo on psychomotor and memory function in normal male volunteers. European Journal of Clinical Pharmacology, 45, 313-320.

Beer, B., Ieni, J., Wu, W-H, Clody, D., Amorusi, P, Rose, J., Mant, T., Gaudreasult, J., Cato, A., and Stern W. (1994). A placebo-controlled evaluation of single, escalating doses of CL 284,846, a non-benzodiazepine hypnotic. Journal of Clinical Pharmacology, 34, 335-344.

Brown, A., Smolensky, M., D'Alonzo, G., & Redman, D. (1990). Actigraphy: a means of assessing circadian patterns in human activity. Chronobiology International, 7, 125-133.

Cantrell, G., & Hartman, B. (1967). Application of time and workload analysis technics to transport flyers. (SAM-TR-67-71). Brooks AFB, TX: USAF School of Aerospace Medicine.

Danjou, P., Paty, I., Fruncillo, R., Worthington, P., Unruh, M., Cevallos, W., & Martin, P. (1999). A comparison of the residual effects of zaleplon [SONATA®] and zolpidem following administration 5 to 2 hr before awakening. British Journal of Clinical Pharmacology, 48, 367-374.

Dinges, D. (1992). Probing the limits of functional capability: The effects of sleep loss on short-duration tasks. In Broughton, R.J.and Ogilvie, R.D. (Eds.), Sleep, Arousal, and Performance, Boston, Birkhäuser, pp. 176-188.

Elie, R., Rüther, E., Farr, I., Emilien, G., & Salinas, E. (1999). Sleep latency is shortened during 4 weeks of treatment with zaleplon, a novel nonbenzodiazepine hypnotic. Journal of Clinical Psychiatry, 60, 536-544.

Ferrara, M., & De Gennaro, L. (2000). The sleep inertia phenomenon during the sleep-wake transition: theoretical and operational issues. Aviation, Space and Environmental Medicine, 71, 843-848.

Ferrara, M., De Gennaro, L., & Bertini, M. (2000). Time-course of sleep inertia upon awakening from nighttime sleep with different sleep homeostasis conditions. Aviation, Space, and Environmental Medicine, 71, 225-229.

Fry, J, Scharf, M., Mangano, R., & Fujimori, M. (2000). Zaleplon improves sleep without producing rebound effects in outpatients with insomnia. International Clinical Psychopharmacology, 15, 141-152.

Hamilton, A, Balnave, R, & Adams, R (1994) Grip strength testing reliability. Journal of Hand Therapy, 7: 163-170.

Hartman, B., & Langdon, D. (1965). A second study on performance upon sudden awakening. USAF School of Aerospace Medicine, SAM-TR-65-61, Brooks Air Force Base, Texas.

Hartman, B., Langdon, D. & McKenzie, R. (1965). A third study on performance upon sudden awakening. USAF School of Aerospace Medicine, SAM-TR-65-63, Brooks Air Force Base, Texas.

Hedner, J., Yaeche, R., Emilien, G., Farr. I., & Salinas, E. (2000). Zaleplon shortens subjective sleep latency and improves subjective sleep quality in elderly patients with insomnia. International Journal of Geriatric Psychiatry, 15, 704-712.

Hindmarch, I., Patat, A., Stanley, N., Paty, I., & Rigney, U. (2001). Residual effects of zaleplon and zolpidem following middle of the night administration five hours to one hour before awakening. Human Psychopharmacology Clinical & Experimental, 16, 159-167.

Hoddes, E., Zarcone, V., Smythe, H., Phillips, R., & Dement, W. (1973). Quantification of sleepiness: A new approach. Psychophysiology, 10, 431-436.

Jasper, H. (1958). Report of the committee on methods of clinical examination in electroencephalography. Electroencephalography and Clinical Neurophysiology, 10, 370-375.

Langdon, D., & Hartman, B. (1962). Performance upon sudden awakening. USAF School of Aerospace Medicine, SAM-TR-62-17, Brooks Air Force Base, Texas.

McNair, D., Lorr, M., & Droppleman, L. (1971). *Manual for the Profile of Mood States*, Educational and Industrial Testing Service (EdITS), San Diego CA.

Patat, A., & Foulhoux, P. (1985). Effect on postural sway of various benzodiazepine tranquillizers. British Journal of Clinical Pharmacology, 20, 9-16.

Perez, W., Masline, P., Ramsey, E., & Urban, K. (1987). Unified Tri-Services Cognitive Performance Assessment Battery: Review and Methodology. Wright-Patterson AFB, Ohio, AAMRL-TR-87-007.

Richardson, G., Carskadon, M., Orav, E., & Dement, W. (1982). Circadian variation of sleep tendency in elderly and young adult subjects. Sleep, 5, S82-S94.

Stone, B. Sleep promoting substances. Neuilly-Sur-Seine, France: NATO; 2001 Report No. RTO-EN-016;9.1-9.20.

Troy, S., Lucki, I., Unruh, M., Cevallos, W., Leister, C., Martin, P., Furlan, P., & Mangano, R. (2000). Comparison of the effects of zaleplon, zolpidem, and triazolam on memory, learning, and psychomotor performance. Journal of Clinical Psychopharmacology, 20, 328-337.

Vermeeren, A., Danjou, P., & O'Hanlon, J. (1998). Residual Effects of Evening and Middle-of-the-Night Administration of Zaleplon 10 and 20 mg on Memory and Actual Driving Performance. Human Psychopharmacology Clinical & Experimental, 13, S98-S107.

Walsh, J., Vogel, G., Scharf, M., Erman, M., Erwin, C., Schweitzer, P., Mangano, R., & Roth, T. (2000). A five-week, polysomnographic assessment of zaleplon 10 mg for the treatment of primary insomnia. Sleep Medicine, 1, 41-49.

Whitmore, J., Fischer Jr., J., Barton, E., & Storm, W. A laboratory evaluation of performance following a daytime nap under zaleplon and placebo conditions. Brooks City-Base, Texas: AFRL; 2003 Technical Report No. AFRL-HE-BR-TR-2003-0053.

Williams, H., & Williams, C. (1966). Nocturnal EEG profiles and performance. Psychophysiology, 3, 164-175.

APPENDIX A
Condition Analyses Table

Test	Outcome Variable	Drug Condition	Baseline (1 hr pre)	Post Drug: Change from Baseline 3.5 hr	4 hr	5 hr	6 hr	7 hr	ANOVA Results: Drug	Drug X Time
Stanford Sleep Scale	Rating	placebo	2.5	0.1	-0.4	-0.1	-0.3	-0.4	Wilcoxon Signed Ranks Tests Used	
		zaleplon	2.6	0.4	-0.2	-0.3	-0.3	-0.4		
Code Substitution (Learning)	Accuracy	placebo	98.36	-1.52	-0.89	-0.89	-1.89	-0.88	F(1,10)= 1.40 P=.265 MSE=20.1	F(4,40)= 1.35 P=.269 MSE=4.3
		zaleplon	96.84	0.50	-0.76	-0.88	0.25	-0.13		
	MRTC	placebo	931.48	117.83	* 84.98	14.67	32.80	* 25.61	F(1,10)= 4.84 P=.052 MSE=23257	$F(2,25)^h$=3.28 P=.045 MSE=11873
		zaleplon	983.08	168.67	-23.01	-58.11	-47.97	-83.73		
	% Omissions	placebo	0	0	0	0	0	0	Wilcoxon Signed Ranks Tests Used	
		zaleplon	0	0.13	0	0	0	0		
	SDRTC	placebo	319.58	84.14	71.47	37.48	63.39	41.35	F(1,10)=1.20 P=.300 MSE=49401	$F(3,28)^h$ = 1.48 P=.242 MSE=16419
		zaleplon	362.18	133.99	12.66	-17.14	-21.05	-42.30		
	Throughput	placebo	65.35	-8.49	* -5.62	-1.49	-2.85	* -1.97	F(1,10)=5.90 P=.036 MSE=95.5	F(4,40)= 1.77 P=.155 MSE=20.4
		zaleplon	61.32	-8.15	0.24	2.82	2.16	5.13		
Code Substitution (Immediate)	Accuracy	placebo	93.94	-3.54	-1.01	-3.03	-3.53	3.03	F(1,10)=.001 P=.972 MSE=224.3	F(4,40)= 1.00 P=.421 MSE=64.4
		zaleplon	93.94	-1.01	-4.04	-1.01	-1.01	-1.51		
	MRTC	placebo	985.22	103.91	91.94	-11.28	43.28	-92.43	F(1,10)=.667 P=.433 MSE=117896	F(4,40) = 2.14 P=.094 MSE=14478
		zaleplon	983.67	144.42	12.79	-129	-78.75	-81.36		
	% Omissions	placebo	0	0	0	0	0	0	Wilcoxon Signed Ranks Tests Used	
		zaleplon	0	0	0	0	0	0		
	SDRTC	placebo	387.80	104.24	102.32	29.47	71.48	-39.01	F(1,10)=.939 P=.355 MSE=125427	F(4,40)= 1.35 P=.269 MSE=33631
		zaleplon	411.74	68.68	74.24	-99.77	-111.13	9.20		
	Throughput	placebo	60.66	-8.59	-4.07	1.37	-5.22	8.14	F(1,10)=1.12 P=.314 MSE=519.2	F(4,40)= 1.82 P=.144 MSE=75.6
		zaleplon	58.48	-6.00	0.21	8.38	6.06	6.00		
Code Substitution (Delayed)	Accuracy	placebo	90.56	-4.72	-9.45	-5.00	-4.45	-0.83	F(1,9)=.043 P=.839 MSE=319.0	F(4,36)= .63 P=.645 MSE=78.3
		zaleplon	90.83	-9.44	-6.39	-5.11	-7.50	0.28		
	MRTC	placebo	1057.87	-18.60	6.02	-7.44	-5.29	-69.14	F(1,9)=.002 P=.965 MSE=145733	$F(3,29)^h$ = .43 P=.623 MSE=17432
		zaleplon	1007.62	32.66	19.67	-11.35	-19.96	-132.87		
	% Omissions	placebo	0	0	0	0	0.28	0.28	Wilcoxon Signed Ranks Tests Used	
		zaleplon	0	0	0	0	0	0		
	SDRTC	placebo	597.30	-89.09	-139.58	-129.60	-84.82	-95.02	F(1,9)=.277 P=.611 MSE=555283	F(4,36)=1.46 P=.234 MSE=32675
		zaleplon	493.56	-16.02	55.82	23.01	-48.04	-152.36		
	Throughput	placebo	55.67	-4.31	-9.53	-4.16	-4.17	1.11	F(1,9)=.824 P=.388 MSE=289.8	F(4,36)= 1.19 P=.331 MSE=68.3
		zaleplon	54.40	-6.74	-4.31	-0.49	-3.27	9.20		
Simple Reaction Time	MRT	placebo	219.30	28.22	4.74	17.38	6.18	-8.91	F(1,10)=2.320 P=.159 MSE=2017.1	F(4,40)= 1.05 P=.394 MSE=562.6
		zaleplon	224.48	6.21	0.65	-5.94	-9.15	-9.38		
	% Omissions	placebo	0	0.45	0	1.36	0	0	Wilcoxon Signed Ranks Tests Used	
		zaleplon	0.91	-0.91	-0.91	-0.91	-0.91	-0.91		
	SDRT	placebo	50.86	17.78	3.13	15.34	9.39	-8.66	F(1,10)=.063 P=.807 MSE=3762.2	$F(2,20)^h$ = 1.01 P=.383 MSE=2265
		zaleplon	48.91	-1.97	21.54	8.33	-0.54	-5.08		

Mathematical Processing	Accuracy	placebo	97.27	-0.36	-0.86	-1.67	-3.56	-2.63	F(1,10)=.136 P=.720 MSE=97.2	F(4,40)= 2.74 P=.042 MSE=5.2
		zaleplon	97.15	-2.60	-2.74	-1.87	-1.76	-3.58		
	MRTC	placebo	1580.61	-19.46	-106.56	-155.12	-226.17	-206.22	F(1,10)=4.289 P=.065 MSE=174462	F(4,40)= 0.96 P=.442 MSE=15426
		zaleplon	1457.50	219.66	80.55	9.19	-100.25	-97.95		
	% Omissions	placebo	0.67	-0.35	-0.53	-0.67	-0.41	-0.34	Wilcoxon Signed Ranks Tests Used	
		zaleplon	0.15	0.36	0.01	0.01	0.16	1.06		
	SDRTC	placebo	554.99	16.61	-5.96	-42.38	-68.52	-26.1	F(1,10)=3.915 P=.076 MSE=64299	F(4,40)= 1.33 P=.275 MSE=10037
		zaleplon	496.45	170.67	105.50	56.01	28.16	-8.28		
	Throughput	placebo	40.30	-1.14	0.77	2.27	4.1	4.52	F(1,10)=2.821 P=.124 MSE=126.1	F(4,40)= 1.13 P=.358 MSE=14.2
		zaleplon	42.97	-6.98	-3.02	-2.24	2.32	2.46		
Matching To Sample	Accuracy	placebo	96.18	-2.14	-4.80	-2.71	0.19	-2.74	F(1,10)=3.861 P=.078 MSE=139.2	F(4,40) = 0.84 P=.511 MSE=44.8
		zaleplon	92.41	3.25	1.67	2.84	0.07	2.09		
	MRTC	placebo	1432.73	-14.05	-32.40	* 99.21	-126.41	* 77.18	F(1,10)=5.945 P=.035 MSE=93917	$F(3,28)^{h}$ = 2.73 P=.066 MSE=64063
		zaleplon	1527.07	-24.18	-149.77	-273.63	-144.07	-117.25		
	% Omissions	placebo	0	0	0	0	0	0	Wilcoxon Signed Ranks Tests Used	
		zaleplon	0	0	0	0	0.57	0		
	SDRTC	placebo	546.18	-14.60	36.89	105.23	-78.61	123.11	F(1,10)=.817 P=.387 MSE=250168	F(4,40)= 2.02 P=.110 MSE=53947
		zaleplon	616.36	97.26	-121.11	-151.62	-94.43	10.73		
	Throughput	placebo	43.58	-2.34	*-3.72	* -1.91	3.82	* -3.38	F(1,10)=12.994 P=.005 MSE=96.7	F(4,40)= 2.58 P=.052 MSE=43.2
		zaleplon	39.10	0.63	5.54	8.44	4.69	6.96		
Symbolic Logical Reasoning	Accuracy	placebo	96.56	-0.31	-0.36	-0.59	-3.21	-2.45	F(1,10)=.691 P=.425 MSE=40.9	$F(2,24)^{h}$ = .21 P=.856 MSE=19.8
		zaleplon	96.15	-2.36	-0.95	-1.57	-4.36	-2.75		
	MRTC	placebo	1555.19	107.57	15.04	-44.53	-140.93	-66.90	F(1,10)=.205 P=.660 MSE=95920	F(4,40)= 1.31 P=.282 MSE=20383
		zaleplon	1530.91	213.24	11.11	-103.98	-49.83	-66.57		
	% Omissions	placebo	0.59	0.16	-0.42	0.37	-0.12	0.42	Wilcoxon Signed Ranks Tests Used	
		zaleplon	0.57	0.63	-0.09	-0.03	0.63	1.34		
	SDRTC	placebo	581.39	74.52	18.97	33.23	17.41	37.73	F(1,10)=.172 P=.687 MSE=98955	F(4,40)= 1.08 P=.377 MSE=12079
		zaleplon	551.04	137.67	54.10	5.93	95.26	13.31		
	Throughput	placebo	40.66	-3.39	-0.93	0.70	1.88	0.80	F(1,10)=.174 P=.685 MSE=75.4	$F(3,30)^{h}$ = .68 P=.571 MSE=18.7
		zaleplon	40.98	-5.7	-1.41	1.88	0.34	0.48		
Psychomotor Vigilance Task	Lapses	placebo	3.91	no	-0.91	0.82	0	0.18	Wilcoxon Signed Ranks Tests Used	
		zaleplon	3.91	data	-1.55	-1.91	0.18	-1.73		
	MRRT	placebo	3.77	no	0.14	-0.09	-0.06	-0.07	F(1,10)=.016 P=.903 MSE=.163	F(3,30)= 2.16 P=.113 MSE=.0234
		zaleplon	3.79	data	0.01	0.02	-0.08	-0.06		
	SDRRT	placebo	0.70	no	-0.03	-0.05	-0.05	-0.02	F(1,10)=.062 P=.808 MSE=.0922	F(3,30)= .22 P=.882 MSE=.0077
		zaleplon	0.72	data	-0.02	-0.01	-0.02	-0.03		

Profile Of Mood States	Anger	placebo	37.82	-0.27	-0.64	-0.55	-0.36	0.09	F(1,10)=.428 P=.523 MSE=22.6	F(2,25)[h] = 1.09 P=.362 MSE=0.961
		zaleplon	38.91	-1.45	-1.00	-0.91	-1.00	-0.36		
	Confusion	placebo	35.73	0.82	-0.09	-1.18	-1.36	-0.91	F(1,10)=.068 P=.799 MSE=38.5	F(4,40)= 1.23 P=.316 MSE=1.866
		zaleplon	35.91	-0.18	-0.82	-1.18	-0.73	-1.36		
	Depression	placebo	38.91	-0.45	-1.00	-1.09	-1.27	-0.91	F(1,10)=.000 P=.987 MSE=34.1	F(2,24)[h] = .219 P=.125 MSE=0.625
		zaleplon	39.09	-1	-0.91	-0.73	-0.91	-1.09		
	Fatigue	placebo	37.09	0.09	-0.45	-2.09	-2.18	-1.73	F(1,10)=.024 P=.881 MSE=18.7	F(3,29)[h] = .273 P=.841 MSE=0.747
		zaleplon	37.00	0	-0.55	-2.27	-2.09	-2.09		
	Tension	placebo	36.09	-1.27	-1.64	-1.73	-1.45	-1.45	F(1,10)=1.040 P=.332 MSE=50.5	F(4,40)= 1.96 P=.119 MSE=0.886
		zaleplon	35.00	-0.64	-0.64	-0.27	0.45	0.45		
	Vigor	placebo	49.00	-0.27	-2.27	-0.27	-0.36	-1.36	F(1,10)=.035 P=.855 MSE=43.7	F(3,29)[h] = .95 P=.447 MSE=15.73
		zaleplon	48.18	-2.18	-2	-0.18	0.45	0.55		
Force Platform	A95 (Eyes open)	placebo	.46	no	0.03	-0.12	-0.07	-0.11	F(1,8)=1.34 P=.281 MSE=.410	F(3,24)[h] = .283 P=.837 MSE=0.022
		zaleplon	.61	data	-0.18	-0.25	-0.27	-0.27		
	A95 (Eyeclosed)	placebo	.54	no	0.02	-0.13	0.17	0.02	F(1,9)=.012 P=.915 MSE=.150	F(1,10)[h] = 1.17 P=.315 MSE=0.212
		zaleplon	.43	data	0.09	-0.06	-0.04	-0.05		
Grip Strength	Max Grip	placebo	45.18	-1.55	-0.45	-0.55	-1.45	-1.55	F(1,10)=2.550 P=.141 MSE=53.9	F(3,32)[h] = 0.51 P=.687 MSE=10.00
		zaleplon	42.91	0.36	1.55	0.55	1.73	1.45		

APPENDIX B
Polysomnography Statistical Table

Variable	Means		SD (diff)	t (9 df)	p (one-tailed)
	Placebo	Zaleplon			
Stage 1 (min)	14.6	15.1	17.1	0.09	.464
Stage 2 (min)	90.1	91.6	34.9	0.14	.446
Stage 3 (min)	11.8	18.9	10.8	2.09	.033*
Stage 4 (min)	25.6	35.1	16.7	1.80	.053
Total Slow Wave Sleep	37.4	54.0	18.0	2.92	.017*
REM (min)	20.8	21.3	16.1	0.10	.462
Sleep Latency (min)	12.6	13.5	10.8	0.26	.396
Time in Bed (min)	213.7	210.9	6.8	1.32	.109
Sleep Efficiency (percent)	76.4	86.6	15.1	2.13	.031*
Total Sleep Time (min)	162.8	182.0	30.2	2.02	.037*

APPENDIX C

Symptom Summary Table

VARIABLE	P-1630	P-1700	P-1800	P-1900	P-2000	Z-1630	Z-1700	Z-1800	Z-1900	Z-2000
Balance	18	0	0	0	0	0	0	0	0	0
Confusion	0	0	0	0	0	0	0	0	0	0
Congestion	9	0	0	0	0	0	0	0	9	9
Dizzy	18	0	0	0	0	18	0	0	0	0
Drowsy	27	9	0	0	0	18	9	0	0	0
Drug-Feeling	9	9	9	0	0	9	0	0	0	0
Dry Mouth	0	0	0	0	0	18	0	0	0	0
Mem-Events	0	0	0	0	0	0	0	0	0	0
Headache	9	9	0	0	0	9	0	0	0	0
Illusions	0	0	0	0	0	0	0	0	0	0
Insomnia	0	0	0	0	0	0	0	0	0	0
Loss-Balance	9	0	0	0	0	0	0	0	0	0
Lightheaded	9	0	0	0	0	9	9	9	0	0
Nausea	9	9	9	0	0	0	0	0	0	0
Diff. Stay Awake	9	9	9	0	0	9	0	0	0	0
Mem-Time	0	0	0	0	0	0	0	0	0	0
Vivid Dreams	9	9	9	9	9	9	0	0	0	0

Numbers indicate the percentage of participants reporting an increase in symptom relative to baseline for each time point (1500-1900 hrs) of each condition (P-placebo, Z-zaleplon).

APPENDIX D
Sleep Inertia Analyses

Test	Outcome Variable	Sleep Inertia ANOVA Time
Stanford Sleep Scale	Rating	Wilcoxon Signed Ranks Tests Used
Code Substitution (Learning)	Accuracy	F(3,30)= 1.31 P=.291 MSE=3.27
	MRTC	F(3,30)= 5.08 P=.006 MSE=6861
	% Omissions	Wilcoxon Signed Ranks Tests Used
	SDRTC	F(3,30)= 2.72 P=.062 MSE=5766
	Throughput	F(3,30)= 5.96 P=.003 MSE=27.7
Code Substitution (Immediate)	Accuracy	F(3,30)= .79 P=.510 MSE=38.86
	MRTC	F(3,30)= 1.69 P=.191 MSE=23630
	% Omissions	Wilcoxon Signed Ranks Tests Used
	SDRTC	$F(2,24)^{b}$=1.15 P=.341 MSE=33647
	Throughput	F(3,30)= 2.92 P=.050 MSE=75.8
Code Substitution (Delayed)	Accuracy	F(3,30)= 2.08 P=.124 MSE=68.60
	MRTC	F(3,30)= .01 P=.999 MSE=30008
	% Omissions	Wilcoxon Signed Ranks Tests Used
	SDRTC	F(3,30)= .63 P=.599 MSE=58113
	Throughput	F(3,30)= 1.62 P=.206 MSE=83.2
Simple Reaction Time	MRT	F(3,30)= 3.20 P=.037 MSE=557
	% Omissions	Wilcoxon Signed Ranks Tests Used
	SDRT	F(3,30)= .88 P=.465 MSE=976
Mathematical Processing	Accuracy	F(3,30)= .74 P=.539 MSE=7.79
	MRTC	F(3,30)= 3.12 P=.040 MSE=18819
	% Omissions	Wilcoxon Signed Ranks Tests Used
	SDRTC	F(3,30)= 1.05 P=.387 MSE=6512
	Throughput	F(3,30)= 1.74 P=.181 MSE=13.0

Matching To Sample	Accuracy	$F(3,30)= .97$ $P=.418$ $MSE=44.1$
	MRTC	$F(3,30)= .91$ $P=.448$ $MSE=41918$
	% Omissions	Wilcoxon Signed Ranks Tests Used
	SDRTC	$F(3,30)= .82$ $P=.492$ $MSE=38305$
	Throughput	$F(3,30)= 1.13$ $P=.355$ $MSE=23.1$
Symbolic Logical Reasoning	Accuracy	$F(3,30)= .11$ $P=.954$ $MSE=5.93$
	MRTC	$F(3,30)= 3.51$ $P=.027$ $MSE=12808$
	% Omissions	Wilcoxon Signed Ranks Tests Used
	SDRTC	$F(3,30)= .90$ $P=.455$ $MSE=12294$
	Throughput	$F(3,30)= 4.05$ $P=.016$ $MSE=8.66$
Psychomotor Vigilance Task	Lapses	Wilcoxon Signed Ranks Tests Used
	MRRT	$F(2,20)= 6.60$ $P=.006$ $MSE=.022$
	SDRRT	$F(2,20)= 1.09$ $P=.357$ $MSE=.006$
Profile Of Mood States	Anger	$F(2,15)^{h} = .95$ $P=.384$ $MSE=1.91$
	Confusion	$F(3,30)= 1.35$ $P=.276$ $MSE=5.48$
	Depression	$F(1,12)^{h} = 1.08$ $P=.335$ $MSE=6.56$
	Fatigue	$F(2,19)^{h} = 1.29$ $P=.298$ $MSE=13.69$
	Tension	$F(1,13)^{h} = 1.56$ $P=.240$ $MSE=9.99$
	Vigor	$F(2,20)^{h} = .374$ $P=.690$ $MSE=49.7$
Force Platform (A95)	Eyes Open	$F(2,16)= .95$ $P=.407$ $MSE=.059$
	Eyes Closed	$F(2,16)= .96$ $P=.404$ $MSE=.057$
Grip Strength	Max Grip	$F(3,30)= .72$ $P=.549$ $MSE=6.50$